

U.S. Serial No.: 10/681,659
Filing Date: October 7, 2003

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REMARKS

Reconsideration is respectfully requested. Claims 1, 2, 4, 9, 10, 12, 15, 17-19 and 22-33 are pending. Claims 3, 5-8, 11, 13, 14, 16, 20, 21, 27 and 28 are canceled. Claims 18, 19, and 22-25 are withdrawn. New claims 29-33 are added. Claims 17 and 26 are amended. Applicants thank the Examiner for the allowance of claims 1, 2 and 4. Cancellation and amendment of the claims does not affect inventorship.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendments

Claims 17 and 26 are amended. New claims 29-33 are added. Support is found in the specification, for example, in paragraphs [00182] to [00189].

Objections to the Specification

The text of the amendment filed on March 1, 2007 has been amended to correct the typographical errors noted by the Examiner in the office action.

Claim Rejection Under 35 U.S.C. § 112

Written Description and Enablement

Claims 9, 10, 12, 15, 17 and 26-28 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description and enablement requirement. Applicants respectfully traverse.

Claims 27 and 28 have been cancelled, thereby rendering the rejections with respect to these claims moot.

Applicants respectfully direct the Examiner to M.P.E.P. 2163, which states:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice.

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The Examiner states that:

[T]he claims are directed to a genus of method, i.e., any method that produces a particular crystal. ...
[O]nly one crystallization method produced the specific crystal in the application....

Applicants respectfully disagree. Claim 9 as amended recites "a protein crystal is formed that has a crystal lattice in a $P2_12_12_1$ space group and unit cell dimensions, $\pm 5\%$, of $a=70.31\text{\AA}$ $b=152.60\text{\AA}$ and $c=214.65\text{\AA}$." Thus, it claims a genus method to grow this specific crystal of a protein. As stated in M.P.E.P. 2163:

A "representative number of species" means that the species which are adequately described are representative of the entire genus.

....

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.... Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

Moreover, as the Examiner can appreciate, at the beginning of this new millennium, the time the instant application was filed, "the skill and knowledge in the art" required for growing crystal had come a long way from the early age of crystallography, or even a decade before then. Kits for large scale screening were widely commercially available, and methods and equipments for robotic large scale screening have been developed by several entities. Due to these developments, large scale screening with minimal amount of protein for conditions to grow crystals became routine, particularly in the industry.

A simple search on Google Scholar for references relating to protein crystallization methods yielded in excess of 30,000 hits most of which had a publication date prior to the filing date of the instant application in 2003. A sampling of the references is provided below. Therefore, it is quite clear that the level of skill in the art was high, with respect to crystallization methods, at the time the application was filed. Hence, a skilled artisan would have been more than capable of arriving at the conditions for crystallization of a protein consisting of "SEQ ID NO:3" or "residues 27-760 of SEQ ID NO:1."

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List of References

- High-throughput protein crystallization** - RC Stevens - Curr. Opin. Struct. Biol, 2000
- Overview of Protein Crystallization Methods**- PC Weber - Methods in enzymology, 1997
- Comparative studies of protein crystallization by vapour-diffusion and microbatch techniques** - NE Chayen - Acta Crystallogr D Biol Crystallogr, 1998
- An approach to rapid protein crystallization using nanodroplets** - DC Uber, EW Cornell, RA Nordmeyer, WF Kolbe, J Jin - J Appl Crystallogr, 2002
- An automated system for micro-batch protein crystallization and screening** - NE Chayen, PD Shaw Stewart, DL Maeder, DM Blow - Journal of Applied Crystallography, 1990
- Protein crystallization for genomics: towards high-throughput optimization techniques** - NE Chayen, E Saridakis - Acta Crystallographica Section D Biological Crystallography, 2002
- Protein Crystallization** - SD Durbin, G Feher - Annual Review of Physical Chemistry, 1996
- System for Evaluating Protein Crystallization Conditions by Microbatch and Vapor-Diffusion Methods** - B Zheng, JD Tice, LS Roach, RF Ismagilov - Angewandte Chemie International Edition, 2004
- Principles of Protein X-Ray Crystallography**- J Drenth - 1999
- Screening of protein crystallization conditions on a microfluidic chip using nanoliter-size droplets** - B Zheng, LS Roach, RF Ismagilov - J Am Chem Soc, 2003
- Protein interactions and crystallization**- DF ROSENBAUM, CF ZUKOSKI - Journal of crystal growth, 1996.
- Protein Crystallization: Micro Techniques Involving Vapor Diffusion**- DR Davies, DM Segal - Methods Enzymol, 1971

As such, at the time the instant application was filed, "the skill and knowledge in the art" had grown into a stage that it was not necessary to disclose each and every condition, foreseeable or unforeseeable, to meet the "representative number" requirement. Description of a representative number of conditions to grow the claimed specific crystal does not require the description of such specificity each growing condition. The wide range of crystallization conditions disclosed by the present invention is sufficient to provide guidance to further explore for new conditions to grow the claimed crystal.

As such, at the time the instant application was filed, "the skill and knowledge in the art" had grown into a stage that it was not necessary to disclose each and every condition, foreseeable or unforeseeable, to meet the "representative number" requirement. Description of a representative number of conditions to grow the claimed specific crystal does not require the description of such specificity each

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growing condition. The wide range of crystallization conditions disclosed by the present invention is sufficient to provide guidance to further explore for new conditions to grow the claimed crystal.

Applicants further submit that a sufficient "representative number" of conditions - the conditions to grow the specific crystal as recited in claim 9- have been provided by the instant application. The specification discloses that the Applicants have undertaken "systematic broad screening crystallization trials on an FAP α complex using the sitting drop techniques" to obtain conditions that appear to produce precipitate and/or crystals. These conditions are used for fine screening for optimal conditions. *See* paragraphs [0088] and [0089]. These experiments led to a thorough understanding of how crystallization conditions affect FAP α crystallization, and a series of crystallization conditions were identified that maybe used to for crystals comprising FAP α . These conditions are summarized in Table 6. The specification further discloses in details one of the crystals obtained under one of the disclosed conditions. *See* Example 2. In addition, the specification disclosed that these crystals could also be obtained with different type of PEG and at different temperatures. *See* Example 2. Therefore, the Applicants have disclosed a wide range of conditions that can be used to grow the claimed specific crystal.

Thus, at the time of the filing, Applicants not only were in possession of the claimed genus method, but also provided sufficient guidance to enable a skilled artisan to practice the claimed method without undue experimentation. As such, the rejection is improper and should be withdrawn.

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CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 442-1000.

Respectfully submitted,

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